The Effects of Vitamin D Supplementation on Bipolar Depression

By

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The Effects of Vitamin D Supplementation on Bipolar Depression

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Abstract

The present study explored the effects of Vitamin D supplementation on symptoms of depression, anxiety, and mania in patients suffering from bipolar disorder. Six participants (four men, two women) enrolled in a 12-week long double-blind randomized study during which they received a Vitamin D supplement or a placebo. At the initial visit, participants’ baseline Vitamin D level was measured. Participants’ depression, anxiety, and mania symptoms were assessed biweekly. Results, at this time, are conducted only on baseline Vitamin D scores because the study is ongoing. A repeated measures ANOVA indicated that baseline Vitamin D levels significantly influenced depression and anxiety symptoms. Moreover, there was a significant decrease in depression and anxiety symptoms experienced by participants between the initial visit and the study’s completion. This change from the study’s start cannot yet be attributed to the Vitamin D supplementation. Better understanding the efficacy of Vitamin D as a treatment for bipolar depression could open new avenues for future treatment options.
The Effects of Vitamin D Supplementation on Bipolar Depression

A mental illness characterized by fluctuations between mood elevations and depressive episodes, bipolar disorder is one that deeply affects individuals through cycles of mania and depression. Manic episodes can be comprised of mood changes, such as experiencing a euphoric high or agitation/irritability, as well as behavioral changes such as restlessness, distractibility, having unrealistic thoughts regarding one’s abilities, acting impulsively, amongst others (National Institute of Mental Health, 2009). Hypomania exists as a less severe version of mania, and while a person may feel productive and energized, their behavior is not as extreme and does not warrant/lead to hospitalization. The depression stage of bipolar disorder, however, can lead an individual to feel low and empty, lose interest in normally enjoyable activities, and for some, experience thoughts of suicide. Individuals can also experienced mixed states, during which they may experience feelings of agitation, significant appetite changes, issues sleeping, and suicidal ideation. These individuals may feel extremely energized, while simultaneously experiencing feelings of hopelessness and despondence.

Patients exhibiting many of these symptoms are diagnosed according to the criteria outlined in the Diagnostic and Statistical Manuel of Mental Disorders (DSM). Bipolar disorder exists in several forms, including bipolar I disorder, bipolar II disorder, and bipolar not-otherwise-specified (NOS). Bipolar I disorder is classified by manic or mixed episodes lasting a minimum of seven days, or by the presence of manic symptoms severe enough to warrant a hospital stay. An individual with this classification must have also experienced depressive episodes (lasting at least two weeks in duration). All of the symptoms present represent significant and noticeable changes to a person’s normal
behavior. Bipolar II disorder is characterized by a pattern of depressive episodes that switch back and forth from hypomanic episodes. With this classification, there is no presence of symptoms indicating full manic or mixed episodes. For a patient to be diagnosed with bipolar NOS, they may exhibit symptoms of the illness, but may not experience them in a long enough duration, or may experience a lesser number of symptoms, than the criteria outlined to be diagnosed with bipolar I or II. These symptoms, similar to other subtypes of bipolar disorder, typically fall outside of the usual range of behavior for that individual. Lastly, cyclothymic disorder is a milder form of bipolar disorder, in which an individual diagnosed experiences a shift in symptoms from hypomaniac episodes to depressive episodes, with these symptoms lasting for a minimum of two years. Because the symptoms are typically milder, the symptoms do not meet the criteria outlined by the DSM for the three subtypes of bipolar disorder (National Institute of Mental Health, 2009).

Symptoms and episodes of bipolar disorder often get worse if proper treatment is not received, and an individual may notice that their episodes become more severe when compared to the severity when their illness first started (Goodwin & Jamison, 2007). Delays in receiving some form of treatment can increase a person’s likelihood of experiencing problems in their social or personal lives, as well as work-related problems (National Depressive and Manic Depressive Association, 2001).

To combat the depressive episodes of bipolar disorder that can inhibit an individual from living their life to their fullest potential, patients can seek medical attention and receive treatment in a variety of forms. Multiple forms of treatment exist to help a patient manage their symptoms to some degree. Medications are an option
available to patients, and include mood stabilizers, atypical antipsychotic medications, and antidepressants. Psychotherapy can also be utilized, with forms such as cognitive behavioral therapy, family-focused therapy, interpersonal/social-rhythm therapy, as well as psychoeducation (National Institute of Mental Health, 2009).

The depression stage of bipolar disorder can often times be extremely difficult to treat, and many of the options available for medication result in unpleasant adverse effects or are lacking evidence of their efficacy in treating the symptoms of depression (Humble, 2010). Further research investigating effective treatment options would improve the general quality of care for these individuals, and research continues to investigate additional ways to both understand bipolar depression as well as to manage it. The current research aims to investigate the role that Vitamin D (serum 25(OH)D) has in bipolar depression and mood elevation.

In the Northeast region of the United States, it is common for members of the population to experience low serum (25(OH)D) because the UVB index is too low for seven months of the year for individuals in this region to synthesize vitamin D from natural light sources. People obtain vitamin D from either food sources or through ultraviolet light, and this vitamin is then hydroxylated to 25-hydroxyl vitamin D (25(OH)D) and is then measured in the serum.

Vitamin D has several mechanisms that have an influence over an individual’s mood. 25(OH)D found in the serum is hydroxylated to calcitrol, or (1,2(OH)2D). Calcitrol has effects through the Vitamin D receptors found in the adult brain. Vitamin D is involved in a number of neurological processes, including nerve growth factor enhancement, neurotransmitter synthesis regulation, as well as other antioxidant
properties (Humble, 2010). Calcitrol is responsible for the activation of the gene expression of enzyme tyrosine hydroxylase, which facilitates the increase in availability of neurotransmitters like dopamine, adrenaline, and neuroadrenaline. These neurotransmitters are known to often play a role in the pathology, or the causes and effects of mood disorders. Calcitrol is also known to enhance nerve growth factor (NGF) and glial derived neurotropic factor (GDNF; Humble, 2010). Research conducted in psychiatry shows that GDNF may play a role in depression (Zhang, et al., 2009), and that vitamin D assists in the brain’s defense system against oxidative degeneration (Humble, 2010).

Past research has started to build the understanding of Vitamin D’s role in the pathology of mood disorders. Clinical studies have demonstrated the association found between low serum (25(OH)D) levels and symptoms of depression, most notably in the population of older adults (Wilkims, et al., 2006). One study demonstrated that adults found to have a lower-baseline serum level experienced increased scores measuring depression when tracked for the three to six years following, in comparison to those measured to have a higher initial baseline (Milanschi, et al., 2010). Additionally, individuals diagnosed with bipolar depression have demonstrated having serum levels lower than the average population in the same area (Berk, et al., 2007).

**The Present Research**

There are few studies investigating associations that may exist between Vitamin D levels and symptoms of depression. Of the studies that do exist, many have strong limitations, such as a small sample size observed, or other issues regarding the methodological procedure (Jorde, et al., 2008). Because of this lack of published studies
that have investigated mood after the supplementation of Vitamin D, the present research study is aiming to further the understanding in this area.

The primary aim of this study is to use a randomized controlled trial to observe changes in serum 25(OH)D levels as well as any changes in symptoms of bipolar depression for individuals who are receiving 5000 IU of Vitamin D3 daily (versus placebo). We predict that an increase in serum 25(OH)D level will lead to improved mood stability resulting from reductions in feelings of depression for participants, who are adults demonstrating an insufficiency of Vitamin D (with a recorded level of less than 30 nanograms/milliliter).

Because the present research study is continuing to collect data through a two-year long randomized, double blind clinical study, this preliminary analysis will instead focus on associations present between initial baseline vitamin D levels (at the start of the participant’s study visits) and symptoms of depression, anxiety, and mania. Because of the association found between low Vitamin D levels and depression symptoms, we predict that lower baseline visit measures of Vitamin D levels in these individuals with bipolar disorder will strongly correlate with increased depressed mood and anxiety measures (Wilkims, et al., 2006).
Method

Participants

A total of six (four males, two females) individuals diagnosed with some form of bipolar disorder (including bipolar I, bipolar II, and bipolar NOS) participated in this research study. Participants were compensated 40 dollars for their time and participation, receiving 20 dollars after the preliminary baseline visit, and 20 dollars upon completion of the study. The mean age of the participants was 53 years. One hundred percent of the participants identified as white/non-Hispanic. All participants provided informed consent prior to participating.

Inclusion and Exclusion Criteria

In order to be eligible to participate in the study, an individual had to be between 25 and 70 years of age. Prior to participating, all participants were diagnosed with some form of bipolar disorder (including type one, type two, and not otherwise specified), and were receiving psychiatric care for the disorder. Eligible participants also needed to have at least a mild level of depression as indicated by a score of seven or greater on the Montgomery-Asberg Depression Rating Scale (MADRS). Following a blood test, participants were eligible only if they had an insufficient level of 25(OH)D serum (Vitamin D) at a level of less than thirty nanograms per milliliter. Because this research is an augmentation study, participants were not excluded based on their medication regimen, nor changes made to their medications throughout the duration of their enrollment.
Several exclusion criteria exist for study enrollment. Patients diagnosed with any systemic diseases were excluded from the study due to the known association of low vitamin D levels and the presence of a systemic disease (Agmon-Levin, et al., 2013). The systemic diseases included: granulomatous, metastatic bone disease, sarcoidosis, Williams syndrome diabetes mellitus, liver and kidney diseases, parathyroid disorder, fat digestion disorder, as well as disorders of vitamin D metabolism. Gastrointestinal surgery also excluded individuals from participating in this study because research demonstrates that fat-soluble vitamin deficiencies can occur following some bariatric surgeries (Slater, et al., 2004). Active suicidality, acute psychosis, or active substance abuse within the last six months can also exclude an individual from participating in the study. Individuals are also ineligible if they are not currently receiving psychiatric care for the treatment of bipolar disorder. While patients were able to maintain current medications they were taking, they were deemed ineligible if they had started a new FDA approved medication regimen for the treatment of bipolar depression (Seroquel, Lamictal, or Symbyax) (or have made changes) within the two weeks prior to the enrollment date. Also ineligible are individuals who have been taking vitamin D replacement therapy within the three months prior to the enrollment date (such as prescriptions of calcitriol, doxercalciferol, and paricalcitol) and adults who are unable to give consent, are incarcerated, or are pregnant.

Design and Materials

The present study is a double blind randomized design for a clinical trial. Participants are given a prescription randomized to be either a placebo (Methyl cellulose capsules) or for vitamin D3 (Cholocalciferol) 5000 IU capsules. Individuals participated in a twelve-week period of bi-weekly appointments following the initial baseline visit.
(during weeks two, four, six, eight, ten and twelve of the study participation period). Upon completion of the study, the change in serum 25 (OH)D from a participant’s baseline visit to their final visit will be evaluated, and will be compared to changes in a participant’s level of depression from the baseline visit to the final visit. Currently the study is in the first year of data collection (it is a two year study in total); therefore, analysis of the changes in serum 25 (OH)D cannot be conducted. However, comparisons to the baseline level of Vitamin D can (and will) be conducted.

**Procedure**

**Screening.** A phone screening with a potential participant was first held to evaluate whether an individual was eligible or ineligible for study participation. This screening took approximately 20 minutes. Further screening for eligibility was then conducted at the initial participant visit to evaluate the Vitamin D level by means of a blood test, to confirm a participant’s diagnosis of bipolar disorder (by conduction of a Structured Clinical Interview for DSM Disorders (SCID) as well as to confirm a participant’s diagnosis of depression (by conduction of the Montgomery-Asberg Depression Rating Scale assessment (MADRS) completed by the research coordinator).

**Baseline (Initial) Visit.** At the first visit, the participant was briefed about the study and offered the opportunity to ask any questions. The participant then provided written informed consent. This baseline visit confirms an individual’s eligibility for the study by assessing the individual’s bipolar diagnosis (SCID), their depressive symptoms (MADRS), and measuring their Vitamin D levels through a blood test.

Once the participant’s blood test results were received, the results were evaluated to determine if the participant’s Vitamin D level is insufficient (below 30 ng/ml).
Additionally, the SCID and MADRS results were evaluated to determine if the participant was eligible. If the participant was Vitamin D insufficient and was deemed to be eligible, they were enrolled in the study and randomly received a prescription for either Vitamin D3 5000 IU or placebo.

After the phlebotomy segment of the initial visit was completed, the research assistant conducted a series of assessments (found below) to collect information from the participant, including the following assessments/forms.

**Demographic Information Questionnaire.** This assessment during the initial baseline visit collected information such as the participant’s age, gender, race, marital status, education, employment status, occupation, income, and menstrual status when applicable.

**Contact Information Form.** The participant’s personal contact information was collected during the baseline visit, in addition to the contact information for their primary care physician and psychiatrist.

**Medication Compliance and Symptom Form.** This assessment, completed at each appointment, tracked medication use and compliance. This tracking documented both study medication as well as other medications that the participant was using. Additionally, adverse effects experienced were recorded to monitor any potential side effects that may have resulted from the study medication use or rare effects of hypervitaminosis (an overdose) of vitamin D.

**Medical Comorbidity Form.** This form, completed at each appointment, assessed the prevalence of the individual’s medical issues, how such issues were treated as well as the affect that these issues had on the individual’s ability to function normally.
This assessment inquired about the presence of other health conditions that the participant might have experienced, including heart disease, high blood pressure, kidney disease, anemia, cancer, thyroid disease, amongst others. The clinical interviewer also noted whether the participant was receiving treatment for the condition (if present), and if limited their activity level.

**Structured Clinical Interview for DSM Disorders (SCID).** Current and past psychiatric disorders were documented by conducting a structured clinical interview that evaluated based on the Diagnostic and Statistical Manual (DSM) IV criterion for diagnosing symptoms. This interview was conducted at the baseline visit only. This study was designed/began prior to the release of the DSM-V in May of 2013. This SCID evaluated the participant’s Axis I disorders (major mental disorders) (First, et. al., 2002). This assessment was utilized to verify a participant’s diagnosis of bipolar disorder (thus, affecting their eligibility).

**Montgomery-Asberg Depression Rating Scale (MADRS).** This scale is a standardized depression rating scale, and assessed the participant’s level of depression at each appointment. This scale assessment is comprised of 10 questions utilized to assess the severity of a participant’s depressive episode. These questions inquire about a series of symptoms, including apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts.

Each question has seven possible responses, ranked from zero to six (For example, for the question evaluating “apparent sadness,” 0 = no sadness, 6 = looks miserable all of the time, extremely despondent). Upon the completion of this
assessment, the clinical interviewer is able to sum the individual question scores to receive an overall depressive measurement score ranging from zero to 60 (Williams & Kobak, 2008). An overall score between zero and six indicates normal/absence of depressive symptoms. A score from seven to 19 indicates mild depression and a score from 20 to 34 indicates moderate depression. A score greater than 34 indicates severe depression (Williams & Kobak, 2008).

A sample question from the MADRS scale is:

Inner Tension: Do you feel tension or edginess only some of the time? Have you been able to handle this tension?

Possible Responses:

0, Placid. Only feeling inner tension
1, Between 0 and 2
2, Occasional feelings of edginess and ill-defined discomfort
3, Between 2 and 4
4, Continuous feelings of inner tension or intermittent panic, which patient can master only with some difficulty
5, Between 4 and 6
6, Unrelenting dread or anguish. Overwhelming panic.

Hamilton Anxiety Scale (HAM-A). This scale measured the severity of a participant’s anxiety. This assessment was completed at each appointment. This is based on 14 parameters, such as tension, fears, anxious mood, insomnia, as well as any somatic complaints (and behavior) highlighted during the interview. These parameters are
evaluated on a scale of zero to four (0: Not present, 1: Mild, 2: Moderate, 3: Severe, 4: Very severe) (Maier, et al., 1988). The total summation of the parameters, giving an overall score measuring the participant’s anxiety, can range from 0 to 56, with a score of less than 17 indicating mild severity of anxiety symptoms, 18 to 24 indicating mild to moderate severity, and 25 to 30 indicating moderate to severe symptoms (Maier, et al., 1988).

A sample component of the HAM-A scale is:

Anxious mood: What’s your mood been like this past week? Have you been anxious, nervous? Have you been worrying? Feeling something bad may happen? Feeling irritable?

Possible Responses:

0, No anxious mood

1, Mild worry or anxiety indicated only on questioning; no change in functioning

2, Preoccupation with minor events, anxiety on as many days as not

3, Near daily episodes of anxiety/worry with disruption of daily activities; daily preoccupation

4, Near constant anxiety; significant role disruption

Young Mania Rating Scale (YMRS). This scale measured mood elevation ratings and evaluated manic symptoms. This assessment was completed at each appointment. It is comprised of 11 questions that allowed the participant to self-report symptoms experienced over the 48 hours prior to their appointment (Young, et al., 1978). Each item in this scale is given a severity ranking. Seven of the questions are evaluated
with answer responses ranging from zero to four, while the remaining four questions are evaluated based on a zero to eight scale, weighting these four questions more heavily. The zero to four scale questions including symptoms such as elevated mood, increased motor activity/energy, sexual interest, sleep, language-thought disorder, appearance, and insight. The zero to eight scale questions are weighted to be more significant to balance out a potential lack of cooperation from very ill patients. These more heavily weighted questions relate to symptoms including irritability, speech, content, and disruptive-aggressive behavior. Upon completion of this scale, the clinical interviewer was able to sum the participant’s responses to acquire an overall mania score. A higher score indicates increased severity of mania, and was tracked bi-weekly over the course of the study (Young, et al., 1978).

A sample component of the YMRS is:

Elevated Mood: This past week how has your mood been?

Responses:

0, Absent

1, Mildly or possibly increased on questioning

2, Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content

3, Elevated, inappropriate to content; humorous

4, Euphoric; inappropriate laughter; singing

Clinical Global Impression of Severity and Improvement (CGI-S CGI-I).

This rating scale measured the severity of symptoms, response to treatment, and
treatment efficacy, and was completed at each appointment. This more subjective scale is typically used for patients with mental disorders and is used by the clinical interviewer at the participant’s time of appointment. Based on how the patient’s illness severity compares to other patients interviewed, the clinician selects a scale number that evaluates the participant’s severity of illness along a 7-point scale (0: Not assessed, 1: Normal, not ill at all, 2: Borderline mentally ill, 3: Mildly ill, 4: Moderately ill, 5, Markedly ill, 6: Severely ill, 7: Among the most extremely ill). Additionally, global improvement is assessed, which evaluates how much the participant improved when compared to the baseline evaluation at the beginning of the study. The clinical interviewer selects a scale number determining the participant’s global improvement off of a 7-point scale (0: Not assessed, 1: Very much improved, 2: Much improved, 3: Minimally improved, 4: No change, 5: Minimally worse, 6: Much worse, 7: Very much worse; Guy, 1976).

**Follow Up Visits.** The participant returned for repeat assessments every two weeks throughout the twelve-week duration of the study. If the participant was unable to come to the appointment, a phone assessment was substituted. Appointments for weeks 2, 4, 6, 8, 10, and 12 lasted approximately 30 to 45 minutes. At the last visit (which took place during week 12 of the participant’s participation in the study) the participant had blood drawn in order to analyze his/her Vitamin D (serum 25(OH)D levels) to evaluate the efficacy of the drug supplementation over the course of the twelve week study.
Results

To examine the data, several different types of analyses were conducted. First, Dependent Means T-Tests were used to examine whether depression, anxiety, and mania scores differed from the start of the study (the baseline visit) to the study’s completion (the final visit during week twelve). Second, correlations were conducted to examine any relationships between baseline Vitamin D levels, depression, anxiety, and mania. Finally, Repeated Measures ANOVAs were conducted to examine whether Vitamin D levels influenced depression, anxiety, and mania scores through the entire study. In other words, this analysis looks at weekly as well as overall changes in depression, anxiety, and mania scores based on levels of Vitamin D (assessed at baseline).

Do Depression, Anxiety, and/or Mania Change Over the 12-week Study? (T-Tests)

**Depression (MADRS).** A Dependent Means t-test was conducted to compare the overall depression score observed during the baseline visit with the overall depression score observed during the study’s final visit in week twelve. Participant’s depression scores were significantly lower at the final visit ($M= 4.50, SD= 5.17$) than at the baseline visit ($M= 19.67, SD= 8.29$), $t (5)= 10.01, p=.00$. See Figure 1 to view the average depression score for participants for each appointment week of the study.

**Anxiety (HAM-A).** As with depression scores, participant’s anxiety scores were significantly lower at the final visit ($M= 4.67, SD= 5.20$) than at the baseline visit ($M= 12.50, SD= 7.74$), $t (5)= 3.81, p=.013$. See Figure 2 to view the average anxiety score for participants for each appointment week of the study.

**Mania (YMRS).** Participant’s mania scores were also significantly lower at the final visit ($M= 1.17, SD= 2.40$) than at the baseline visit ($M= 8.50, SD= 6.53$), $t (5)= 2.53$,
$p = .052$. See Figure 3 to view the average mania score for participants for each appointment week of the study.

Overall, these findings suggest that participants saw relief in their symptoms of depression, anxiety, and mania over the 12-week study period, regardless of their Vitamin D levels. Since these participants need to be seeing a clinician for their bipolar disorder to be eligible for the study, these findings suggest that something is helping them over the 12-weeks of being in the study—whether it is being in the study or seeking clinical help, we are unable to tell at this time.

**Is There a Relationship Between Baseline Vitamin D Levels and Overall Depression, Anxiety, or Mania Scores? (Correlations)**

Pearson product-moment correlation coefficients were computed in order to assess the relationship between the average depression, anxiety, and mania scores over the course of the study and the baseline Vitamin D level recorded for each participant.

**Depression and Vitamin D Baseline.** Contrary to our expectations, the negative correlation between baseline Vitamin D level and depression was not statistically significant, $r = -0.709, n = 6, p = .115$. While not significant, we still looked at the correlation pattern and found that the negative correlation suggests that higher levels of Vitamin D relate to lower depression scores (see Figure 4 for this correlation).

**Anxiety and Vitamin D Baseline.** There was a also a fairly strong, but marginally significant, negative correlation between the overall anxiety score and the baseline Vitamin D level, $r = -0.735, n = 6, p = 0.096$. This correlation suggests that when the baseline Vitamin D level is higher, then the anxiety level (and presence of symptoms associated with anxiety) tends to be lower (see Figure 5 for this correlation).
**Mania and Vitamin D Baseline.** There was a significant strong negative correlation between the overall mania score and the baseline Vitamin D level, \( r = -0.94, n = 6, p = .005 \). These results indicate that when the baseline Vitamin D level is higher, the mania level (and presence of symptoms associated with mania) is lower, or vice versa (see Figure 6 for this correlation).

**Depression, Anxiety, and Mania.** The relationship between Depression, Anxiety, and Mania was also examined. Results show a significant and strong positive correlation between the overall anxiety score and the overall depression score, \( r = 0.979, n = 6, p = .001 \). These results indicate a strong relationship between symptoms of depression and symptoms of anxiety, and that anxiety symptoms (and overall score) could act as a strong predictor of depression symptoms, and vice versa. However, there was no relationship between depression and mania \( (p > .131) \) or between anxiety and mania \( (p > .124) \).

**Do Baseline Vitamin D levels influence Depression, Anxiety, and Mania over 12-weeks (Repeated Measures ANOVA)?**

Prior to running the Repeated Measures ANOVA, we conducted a median split (Median = 19.5) on the baseline levels of Vitamin D. From this analysis, we were able to divide the participants into two groups—those with lower and those with higher levels of baseline Vitamin D. This variable became the between-participants factor and the scores of depression, anxiety, and mania during each visit were the within-participants factors.

**Depression.** There was a significant within-participant effect for change in bi-weekly depression scores over the course of the twelve-week study, \( F (1,6) = 8.51, p = .00 \). A post-hoc pairwise analysis was conducted to further analyze the differences in
depression scores from week to week. A significant difference was found between the baseline week depression score and each bi-weekly measurement until the end of the study (p’s < .04, see Table 1 for the post-hoc comparisons). In every case, the baseline depression score was higher than the subsequent week’s score. There were no significant differences in any other bi-weekly score comparisons (e.g., week two and week eight), ps > .104.

However, there was no interaction between depression scores over the course of the study and Vitamin D levels, p > .573. There was, however, a significant between-participants effect of Vitamin D levels on the overall depression score, such that those with higher levels of Vitamin D at baseline (M= 4.095, SE= 1.648) had lower depression scores than those with lower levels of Vitamin D at baseline (M= 16.714, SE= 1.648), F (1, 6) = 29.32, p = .006.

**Anxiety.** There was also a significant within-participant effect for change in bi-weekly anxiety scores over the course of the twelve-week study, F (1,6) = 5.04, p = .002. Post-hoc pairwise analyses showed a significant difference between the baseline week anxiety score and weeks four, six, 10, and 12 (ps <.03). There were marginal differences between baseline and weeks two and eight (ps <.09). In all cases, the baseline anxiety score was higher (or tended to be higher) than the subsequent weeks. As with depression scores, there were no significant differences in any other bi-weekly score comparisons (e.g., week two and week eight), ps > .112. See Table 2 for the post-hoc analyses.

As with depression scores, there was no interaction between anxiety scores over the course of the study and Vitamin D levels, p > .558. There was, again, a significant between-participant effect of Vitamin D levels on the overall anxiety score, such that
those with higher levels of Vitamin D ($M=1.57$, $SE=1.27$) had lower anxiety scores than those with lower levels of Vitamin D ($M=5.62$, $SE=1.27$), $F(1,6) = 59.44$, $p = .014$.

**Mania.** There was a significant within participants effect for change in mania scores over the 12-week study, as the mania score was lowered for an individual, $F(1,6) = 3.98$, $p = .007$. A post-hoc pairwise analysis was conducted to further analyze the differences in mania scores from week to week. A significant difference was found between the baseline week mania score and week 6 ($p = .031$) and week 10 ($p = .009$). Between the baseline visit until the end of the study ($p = .057$) a marginally significant difference was observed ($ps < .09$, see Table 3 for the post-hoc comparisons). In every case, the baseline mania score was higher (or tended to be higher) than the subsequent weeks. There were no significant differences in any other bi-weekly score comparisons (e.g., week two and week eight), $ps > .123$.

However, there was no interaction between mania scores over the course of the study and Vitamin D levels, $p > .384$. There was a significant between-participants effect of Vitamin D levels on the overall mania score, such that those with higher levels of Vitamin D ($M=3.52$, $SE=1.39$) had lower mania scores than those with lower levels of Vitamin D ($M=11.67$, $SE=1.39$), $F(1,6)=15.99$, $p = .016$.

**Discussion**

While a significant correlational relationship between the baseline Vitamin D level and the overall depression score was not observed, significant relationships were observed between these baseline Vitamin D levels and symptoms of both anxiety and mania. Overall, the lower the initial Vitamin D baseline was observed to be in a
participant, then the higher the level of anxiety and mania was recorded for the participant.

Additionally, despite the absence of a correlation between the baseline Vitamin D level and the overall depression score, the baseline Vitamin D level was found to have a statistically significant effect on the overall depression average throughout the course of the study. More specifically and as found in past research (Wilkims, et al., 2006), those with higher baseline levels of Vitamin D experienced less severe symptoms of depression—even though all participants were experiencing the depression stage of bipolar disorder.

Past research also suggests that anxiety disorders are often comorbid with bipolar disorder (Krishnan, 2005). This is consistent with our finding that there was a strong positive relationship between depression and anxiety. In other words, the more depressed an individual was, then the more anxiety they experienced as well, and vice versa.

While not examined in the context of bipolar depression in previous research, we also found a similar effect between baseline Vitamin D levels and the overall anxiety score as well as overall mania score. Again, the findings suggest that those with higher baseline levels of Vitamin D experienced less severe symptoms of anxiety and also mania.

One limitation of the current work is that this study is ongoing, and is continuing to collect data and recruit more participants at the present time. Therefore, the data collected and reported in this paper only represents the preliminary pool of participants, and does not reflect the total number of participants that will be enrolled/will have completed the study throughout the entirety of the study’s execution. Thus, the current
results and analyses may not best reflect the population from which we are recruiting. However, the collection of additional participants will enhance the limited sample size ($N = 6$) for future analyses.

Another limitation is that because this study is structured as a randomized double-blind clinical study, the condition that each participant was placed in (either receiving the study medication, a Vitamin D supplement, or simply a placebo) cannot be revealed until the study’s completion. Because of this, the influence of the Vitamin D supplementation on improvement of symptoms of the depressive stage of bipolar disorder could not be completed in this preliminary set of analyses. Although we cannot yet determine the randomly assigned medication for each participant, we are noticing a decrease in scores for depression, anxiety, and mania symptoms across all participants as they progress through the study. It is possible that because all participants are receiving psychiatric care throughout the study’s duration, this decrease in symptoms could be attributed to improvement in their condition as a result of the care they are receiving. It is also possible that participating in the study and meeting bi-weekly (whether in-person or over the phone) is also contributing to this finding. Future analyses will be able to better distinguish the effect of the Vitamin D supplementation on overall scores for symptoms of depression.

While some past research has investigated the retrospective relationship between Vitamin D levels and symptoms of depression, the present study provides the opportunity to directly observe the potential effects of this supplement on symptoms, specifically for those experiencing the depressive stage of bipolar disorder. Further insight into this relationship may open up future avenues for treatment as healthcare providers attempt to
assist their patients as effectively as possible. Because symptoms of depression and symptoms of anxiety were so closely correlated, future research could also explore whether the supplementation of Vitamin D lessens symptoms of anxiety over time. Because the present study has also demonstrated a significant change in mania symptoms throughout the course of the study, it is possible that the Vitamin D supplementation could be having an effect on symptoms of mania. Research could be extended to evaluate the effect of this supplementation on those experiencing the manic stage of bipolar disorder. Utilizing Vitamin D as a form of treatment for bipolar depression requires further exploration, however, the present study begins to increase our awareness regarding the potential of the supplement. These preliminary analyses have both highlighted the relationship between the initial baseline Vitamin D level and the symptoms of bipolar depression and have demonstrated that this baseline may have an effect on symptoms including depression, anxiety, and mania. Such steps have laid a foundation for future analyses to build from to further our understanding of Vitamin D as a treatment option.
References


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### Tables

**Table 1**

*Changes in Depression Scores Over Study*

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Table 2

*Changes in Anxiety Scores Over Study*

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### Table 3

*Changes in Mania Scores Over Study*

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Figure 1. The average depression score recorded for participants at each visit (from the baseline visit to week 12).
Figure 2. The average anxiety score recorded for participants at each visit (from the baseline visit to week 12).
Figure 3. The average mania score recorded for participants at each visit (from the baseline visit to week 12).
Figure 4. The average depression score for participants with varying baseline Vitamin D levels.
Figure 5. The average anxiety score for participants with varying baseline Vitamin D levels.
Figure 6. The average mania score for participants with varying baseline Vitamin D levels.